UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/463,733 | 06/12/2000 | CHARLES ZUKER | 02307E-085110US | 6739 |

7590 08/31/2007

ANNETTE S PARENT
TOWNSEND AND TOWSEND AND CREW
TWO EMBARCADERO CENTER
8TH FLOOR
SAN FRANCISCO, CA 94111

| EXAMINER | |
|---|---|
| MYERS, CARLA J | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 08/31/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/463,733 | ZUKER, CHARLES | |
| | Examiner | Art Unit | |
| | Carla Myers | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *13 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,5-13,15,17,19,20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-13,15,17,19,20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on June 13, 2007 has been entered.

Claims 1, 5-13, 15, 17, 19, 20, and 22 are pending and have been examined herein.

This action contains new grounds of rejection necessitated by Applicant's amendments to the claims. This action is made non-final.

### New Grounds of Objection

2. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

The specification as originally filed does not appear to provide proper antecedent basis for the recitation in claims 1, 5-13, 15, 17, 19, 20 and 22 of a method of screening for a modulator of RDGC GPCR phosphatase activity wherein the method comprises providing a second sample comprising rhodopsin G protein coupled receptor and a mutant Drosophila RDGC phosphatase and comparing the level of Drosophila RDGC

phosphatase activity in the first and second sample to thereby detect RDGC GPCR phosphatase activity and to detect a modulator of RDGC GPCR phosphatase activity. As noted in the response of June 13, 2007, originally filed claim 14 recites a method of screening for a modulator of RDGC GPCR phosphatase activity wherein the method comprises a step of providing a second sample comprising rhodopsin G protein coupled receptor and a mutant Drosophila RDGC phosphatase and comparing the level of Drosophila RDGC phosphatase activity in the first and second sample to thereby detect RDGC GPCR phosphatase activity and to detect a modulator of RDGC GPCR phosphatase activity. However, the specification does not appear to provide proper antecedent basis for these limitations.

**New Grounds of Rejection**

**Claim Rejections - 35 USC § 112 – Written Description**

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-13, 15, 17, 19, 20, and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analyzing claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note that with regard to

genus/species situations, a "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof.

Thereby, to ascertain whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. It is then determined whether a representative number of species have been defined by other identifying characteristics.

In the present situation, The claims are drawn to a method for screening for modulators of RDGC GPCR phosphatase activity, wherein the method requires providing a second sample comprising a mutant Drosophila RDGC phosphatase. The claims do not define the mutant Drosophila RDGC phosphatase in terms of any particular structural properties. Further, the claims do not define the functional properties of the mutant RDGC phosphatase. Accordingly, the claims have been given their broadest reasonable interpretation as including mutants with activity which is

increased or decreased or absent relative to wildtype Drosophila RDGC phosphatase and mutants which have the same activity as wildtype Drosophila RDGC phosphatase. Additionally, the recitation of "Drosophila" is not considered to impart any particular structural limitation onto the claimed mutant since such a recitation includes proteins directly isolated from drosophila as well as any protein whose sequence was derived from any source, but which was expressed in drosophila.

The specification (page 8) broadly defines a RDGC phosphatase as including polymorphic variants, alleles, mutants, and closely related interspecies variants that have at least 60% identity at the amino acid level to a RDGC phosphatase and which have GPCR phosphatase activity. The originally filed specification (page 8) cited Steele et al (Cell (1992) 69:669-676) as teaching the amino acid sequence of Drosophila RDGC phosphatase. The specific amino acid sequence disclosed by Steele has been added to the specification as SEQ ID NO: 1. Regarding mutants, the specification (pages 43-45) discloses a method in which GPCR phosphatase activity is assayed in rdgC mutants. The specification (page 44) states that "rdgC is a mutation in the RDGC phosphatase gene." At page 4, the specification refers to the results obtained with "rdgC double mutants." The specification (pages 45-46) also discloses a method in which RDGC mutant flies are analyzed for their deactivation kinetics. However, the specification does not disclose the specific structure of the RDGC mutant protein or nucleic acid encoding said protein. The prior art of Byk (PNAS. 1993. 90: 1907-1911) discloses an eye preparation from Drosophila comprising the retinal degeneration C (rdgC) mutant (page 1908). The specification does not appear to specifically

contemplate this particular source of Drosophila eye preparations containing the retinal degeneration C (rdgC) mutant disclosed by Byk. Thereby, the specification cannot be relied upon for providing support for this particular mutant..

Accordingly, no mutant Drosophila RDGC phosphatases have been sufficiently described in terms of their specific and complete chemical structure. Further, no additional mutants within the broadly claimed genus have been described in terms of any other relevant identifying characteristics (e.g. source of the protein, functional activity, molecular weight, etc.).

Thus, Applicant has not disclosed a representative number of species within the broadly claimed genus of Drosophila RDGC phosphatase mutants.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y.,2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of the current claims comprises the use of mutant RDGC phosphatase which the present inventors were not in the possession of, or which were not known to the inventors.

As noted in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), the Federal Circuit concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

With respect to the present invention, there is no record or description which would demonstrate conception of a representative number of mutant RDGC phosphatases, including homologues, allelic variants, and mutants of SEQ ID NO: 1 obtained from any organism and having activities greater than, less than or identical to the wildtype RDGC of SEQ ID NO: 1. Therefore, the claims fail to meet the written description requirement because the claims encompass a significantly large genus of mutant RDGC phosphatase sequences which are not described in the specification.

**Claim Rejections - 35 USC § 112, second paragraph**

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, and 5-13 are indefinite over the recitation of "the rhodopsin" because this phrase lacks proper antecedent basis. While the claims previously refer to a

"rhodopsin G protein coupled receptor," the claims do not previously refer more generally to "a rhodopsin."

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-13, 15,17, 19, 20, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Byk (PNAS. 1993. 93: 1907-1911; cited in the IDS as reference "AD") in view of Zuker (PNAS. 1996. 93: 571-576; cited in the IDS as reference "AG"), Fang (U.S. Patent No. 5,693,488) and Steele (Cell. 1992. 69:669-676; cited in the IDS as reference "AF").

Byk teaches a method of screening *in vitro* for compounds which modulate RDGC GPCR phosphatase activity wherein the method comprises: i) providing a first sample of eye membranes containing wild-type RDGC; ii) contacting the first sample with a test compound; iii) providing a second sample of eye membranes containing mutant RDGC; iv) contacting the second sample with a test compound; v) detecting Drosophila RDGC GPCR phosphatase activity in the first and second sample; and comparing the level of Drosophila RDGC GPCR phosphatase activity in the first and second sample, thereby identifying a modulator of RDGC GPCR phosphatase activity (see page 1909, and figures 2 and 5). Further, Byk teaches that the GPCR rhodopsin is a major substrate for RDGC phosphatase (page 1908). As stated by Byk (page 1910),

following phosphorylation of rhodopsin and release of arrestin, "p-R then becomes an efficient substrate for rhodopsin phosphatase, which safely reintroduces it to the rhodopsin pool, ready for the next round of photoexcitation." The reference further states (page 1910) that "(g)enetic analysis of the *Drosophila* mutant rdgC revealed that retinal degeneration is dependent on high levels of activated rhodopsin and placed the site of action of the *rdgC* gene product before phospholipase C."

In the method of Byk, the test compounds calcium and arrestin are used to assay for their ability to modulate dephosphorylation of rhodopsin by RDGC phosphatase. Byk does not specifically teach performing the screening assay using a test compound that is a RDGC phosphatase mimetic.

However, Zuker teaches a method of measuring membrane potential changes in intact *Drosophila* photoreceptor cells and calcium changes in *Drosophila* transgenic for a particular rhodopsin (Figure 4). Zuker (page 571) teaches that activated rhodopsin (metarhodopsin) activates a heterotrimeric G protein, which in turn activates phospholipase C encoded by the norpA gene. The phosopholipase C then catalyzes the breakdown of $PIP_2$, ultimately leading to the opening of cation-selective channels and the generation of a depolarizing receptor potential. In the illustration set forth in Figure 1 of Zuker shows that rhodopsin is dephosphorylated by RDGC phosphatase. At page 575, Zuker states that "the genetic dissection of this [phototransduction] pathway in humans and flies has provided fundamental insight into the molecular and cellular basis of inherited retinal disorders". Zuker (page 575) further states that "It is here where the study of phototransduction in *Drosophila* offers unprecedented versatility. The study of

this signal cascade in the fruit fly *Drosophila melanogaster* makes it possible to use powerful molecular genetic techniques to identify novel transduction molecules and then to examine the function of these molecules *in vivo*, in their normal cellular and organismal environment". Thereby, Zuker provides the motivation to identify additional molecules that effect the dephosphorylation and phosphorylation of rhodopsin to further analyze and understand the response of a photoreceptor cell.

Fang teaches methods for identifying ligand agonists and antagonists which act as natural mimetics of phosphatases (col. 4 and 20). Fang teaches that it is conventional in the art at the time the invention was made to screen for mimetics of a phosphatase in order to identify agonists or antagonists of a phosphatase (col. 20) .Fang also teaches that methods were well known in the prior art for generating mimetics and for screening to identify mimetics and to elucidate their effects on phosphatase activity (col. 20 and 21).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Byk so as to have used RDGC mimetics in place of calcium or arrestin in order to have provided a method for identifying mimetics that modulate dephosophorylation of rhodopsin, thereby providing a means for further studying the phototransduction process and for obtaining mimetics that act as agonists or antagonists of RDGC phosphatase.

Additionally, Byk does not disclose the sequence of the Drosophila RDGC phosphatase used in the assay and thereby does not specifically teach that the RDGC phosphatase consists of the sequence of SEQ ID NO: 1.

However, Steele (Cell. 1992. 69:669-676) discloses the cloning of drosophila RDGC phosphatase and teaches the complete sequence of Drosophila RDGC phosphatase which is identical to present SEQ ID NO: 1 (see, e.g., page 671).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have specifically used the Drosophila RDGC phosphatase disclosed by Steele consisting of the sequence of present SEQ ID NO: 1 in the method of screening for modulators of RDGC phosphatase because this protein constitutes wildtype Drosophila RDGC phosphatase and thereby would have provided the most effective RDGC phosphatase for use in assays to screen for modulators of this phosphatase.

Regarding claims 5 and 17, Byk does not teach performing the screening assay using recombinant rhodopsin. However, the recitation in the claims of "recombinant" does not further distinguish the claimed RDGC phosphatase over the naturally occurring phosphatase. The claims and specification do not recite any identifying characteristics which would distinguish recombinant RDGC phosphatase from naturally occurring RDGC phosphatase. Therefore, this recitation is not considered to further limit the claimed subject matter. Furthermore, nucleic acids encoding rhodopsin were well known in the art at the time the invention was made, as was the use of such nucleic acids to synthesize recombinant proteins. In particular, Zuker (page 572-573) teaches the use of recombinant rhodopsin in assays to monitor G-protein coupled receptor phosphorylation. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Byk so as to

have used recombinant rhodopsin in place of native rhodopsin in order to have provided a convenient means for obtaining sufficient quantities of rhodopsin protein to use in *in vitro* and *in vivo* assays.

Regarding claims 6 and 7, Byk teaches detecting RDGC GPCR phosphatase activity by means of a phosphorylation assay that is conducted by measuring mobility on an electrophoretic gel (see figures 2 and 5, and page 1909).

Regarding claims 8-12, 15, 17, 19, 20 and 22, Byk does not teach applying the screening method to one performed in a cell or *in vivo.*

However, as discussed above, Zuker exemplifies transgenic Drosophila which express recombinant rhodopsin and teaches the benefits of using transgenic Drosophila to analyze in vivo activities. Zucker (page 575) teaches studying the phototransduction signaling pathway in Drosophila is especially valuable because such methodology can be performed in intact cells or organisms, thereby allowing for the examination of the function of the signaling molecules *in vivo*, in their normal cellular and organismal environment.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have transformed isolated cells, particularly insect cells, with expression vectors comprising rhodopsin and RDGC nucleic acids since Byk teaches that rhodopsin and RDGC proteins are involved in the phototransduction signal cascade and because this would have achieved the advantage of using an isolated system in which the presence of a particular pathway component could be controlled and the expressed proteins would be in an environment similar to the normal cellular

environment (i.e., in an insect cell). Further, Zuker teaches the advantages of the ability to dissect pathways molecularly. To most closely mimic a natural environment, it would have been desirable and obvious to one of ordinary skill in the art at the time the invention was made to have used whole Drosophila cells and transgenic organisms in the method of Byk instead of membrane preparations because Zuker teaches that light and calcium applied to whole cells can be used as methods of screening for compounds which influence the phototransduction pathway (see, for example, Figure 3) and Zuker teaches the importance of assaying molecular mechanisms *in vivo* in their normal cellular and organismal environment.

Additionally, regarding claim 8, Byk does not teach detecting RDGC GPCR phosphatase activity by performing a G-coupled receptor signal transduction assay. However, as discussed above, Zuker (pages 572-573) teaches monitoring RDGC GPCR phosphatase activity by performing G-coupled receptor signal transduction assays in situ and in vivo. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Byk so as to have assayed for RDGC phosphatase activity using the assays of Zuker in order to have provided an effective means for screening for RDGC mimetics in situ or in vivo to achieve the advantage of performing the screening assay in a molecular environment that more closely resembled the normal cellular and organismal environment.

Regarding claims 13 and 22, Byk teaches providing a first and second membrane preparation in a water based homogenization buffer and thereby is considered to teach providing a first and second aqueous sample

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

/Carla Myers/
Primary Examiner, Art Unit 1634